metabolism is reduced in patients with preexisting liver disease and statins are known to increase ALT [3,4], with a slight dose dependency of ALT increase for higher statin doses ([4], Table 3).

At no time did Björnsson *et al.* [2] claim a dose dependent statin hepatotoxicity, but described a rare, severe idiosyncratic statin hepatotoxicity; reexposure with similar symptoms nearly proves a causal relationship. Bader should have withdrawn his previous statement concerning the myth of statin hepatotoxicity [5], because this proposal was incorrect and misleading; considering the very low incidence in clinical studies, spontaneous reports, and case reports, the decision still will result in prescribing statins rather than withholding them.

Most systems to detect rare ADRs rely upon active reporting systems where cases are only included if physicians suspect a causal relationship. These systems are heavily biased toward assuming causality even if this does not exist; the dilemma of prejudice and selective data reporting, as is prevalent for other cases of potential hepatotoxicity by drugs and herbs, was elegantly solved by Björnsson *et al.* using the diagnostic algorithm of CIOMS, also called RUCAM [2]. Despite its known shortcomings, this causality assessment method has been used extensively to evaluate hepatotoxicity by drugs [6]. In relation to the study on statin hepatotoxicity by Björnsson *et al.* [2], the applied method of CIOMS/RUCAM was considered the best method available for this inquiry [1].

Björnsson *et al.* [2] identified cases of idiosyncratic hepatotoxicity due to statins and discussed their results regarding previous reports on other cases of statin hepatotoxicity. This confirms that package inserts of warnings about the rare hepatotoxicity problem should remain, as opposed to the viewpoint of Bader who prefers its deletion [5]. The cautionary statement is valuable information for physicians and patients and a preventive measure for legal consequences that otherwise may reach statin manufacturers in cases of statin hepatotoxicity.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Statin hepatotoxicity and the dilemma of causality in rare hepatic adverse drug reactions"

To the Editor:

ALT monitoring for statins no longer recommended

It is gratifying that since the publication of my editorial review on statins and the liver (February 2012 issue of the *Journal*), the USA Food and Drug Administration (FDA) announced on 28 February 2012, a marked relaxation of package insert language on all statins [1]. Since pharmaceutical safety boards of many countries closely follow the insert language of the FDA, these revisions will be of interest to a worldwide audience.

What was previously a hodge-podge of comments about the liver that differed for each statin, the discussion has been greatly redacted and made uniform. Briefly, the statin labels no longer recommend ALT monitoring after starting a statin. Should acute liver disease develop, the statin should be withheld until the cause is ascertained. This would imply that the patient should be told before treatment about possible signs of drug-induced liver injury and urged to inform the physician if these symptoms occur. The label reminds the reader that an ALT elevation can also occur from muscle injury.

These changes represent a seismic shift in policy. The FDA clearly agrees that an elevated ALT after initiating a statin is not a sign of hepatotoxicity. Instead, the shift in monitoring for symptoms follows the same successful approach as for isoniazid monitoring. I have advocated these changes for some time [2–4].

Still, the labels advise that liver tests be checked prior to initiating a statin, and that statins should not be given to patients with "active liver disease." The phrase "active liver disease" is not defined on the label nor anywhere else I am aware of.

The correspondents and I both agree that statins can be given to patients with chronic liver disease. There is reasonable disagreement over use in decompensated liver patients simply due to a lack of data. However, data are starting to appear. In Spain, Abraldes *et al.* gave 40 mg of simvastatin or placebo to 60 cirrhotics with portal hypertension (proved by WHVP) in a randomized

controlled fashion over 30 days. The intervention group experienced a significant decrease in portal hypertension that was additive to the effects of propranolol. Moreover, liver tests increased more often with placebo than simvastatin [5].

The correspondents generalize, without support, that non-USA physicians have no trouble giving statins to patients with liver disease. In the editorial, I cite an international HCV treatment study where the majority of authors are not from the USA [6]. Only 3% of the 403 patients were on statins; whereas, given the customary age range for participants in HCV studies, one would expect 30% or more of these latter study patients to need a statin. These data would seem to indicate a bias by hepatologists worldwide not to give statins to patients who have at least hepatitis C disease.

The problem the correspondents fail to apprehend with RUCAM methodology is its extremely low positive predictive value (PPV). With RUCAM, the probability of a statin being correctly identified as the "true" cause of idiopathic test abnormalities is less than 1% [4]. That is, if the RUCAM determines the statin is the culprit, 99 out of a 100 times it is wrong. Not the type of certainty one would want in a court of law, for example. While this level of uncertainty may be sufficient to withdraw a drug from a patient, it is not compelling enough to conclude scientifically that statins cause idiosyncratic reactions. Thus, there remains legitimate doubt as to whether statins are responsible for rare instances of idiosyncrasy. All of the cases presented by Bjornsson *et al.* could easily be counted as background noise [7]. Nevertheless, until we become more scientific and settle the issue with proteomics and microarray testing, we are stuck with clinical opinion; the variations of RUCAM represent only attempts to score clinical judgment with numbers.

The terminology for the subject is critical otherwise the reader will confuse what the message of statin mythology has been all about. The letter writers use the term "hepatotoxicity" both as a general term, and for predictable dose-dependent reactions. I believe universal practice is to now use "DILI" or "drug-induced liver injury" as a general term, and restrict hepatotoxicity to the predictable, dose-dependent setting [8].

The remaining concerns of the correspondents have become moot since the revisions of 28 February 2012 by the FDA.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Which is the real efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in HCV infected patients with advanced fibrosis?

To the Editor:

We have read with great interest the article of Prati *et al.* [1]. The authors concluded that patients infected with HCV genotypes 1–4 that received PegIFNα-2A plus ribavirin with advanced fibrosis (staging $\geqslant 3$ according to Ishak classification) had an end treatment response (ETR) and sustained virological response (SVR) rates that were not influenced by fibrosis stage. In contrast, PegIFNα-2B plus ribavirin was less effective than PegIFNα-2A and led to a lower rate of both ETR and SVR in patients with staging $\geqslant 3$. We are concerned about part of the content of the paper. The article analyzed a heterogeneous population of patients infected with HCV that included "difficult to treat patients" infected with genotypes 1–4 and "easy to treat patients" infected with genotypes 2 and 3. Those infected with HCV genotypes 1-4 were analyzed together and stratified according to the Ishak classification staging score. However, several questions remain unanswered: What was the distribution of patients with genotype 4 in the different staging groups? What was the percentage of Egyptian patients in the genotype 4 group included in the study? In Northern Italy, HCV genotype 4 was reported in about 2% of all patients infected with HCV [2]. In addition, different studies have reported that patients infected with genotype 4 presented a better SVR compared to those infected with genotype 1, particularly in patients that achieved a rapid virological response (RVR) [3,4]. Furthermore, Egyptian patients infected with genotype 4 with advanced fibrosis had a better SVR compared to European and